International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Issue 3, 2025

Review Article

SPRAY DOSAGE FORMS: A PROMISING APPROACH TO SYSTEMIC PHARMACOTHERAPY

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Received: 13 Dec 2024, Revised and Accepted: 23 Mar 2025

ABSTRACT

This article discusses the development of spray medications as a novel and promising approach in therapy, focusing on their advantages, disadvantages, and potential applications. The main idea highlights the importance of innovative drug delivery systems, such as spray formulations, in modern medicine. The article reviews various studies and evaluates the effectiveness of sprays in systemic therapy, emphasizing their benefits in terms of rapid drug action, reduced side effects, patient compliance, dosing accuracy, and convenience of use. This method has several significant advantages: a fast onset of action; for example, nitroglycerin absorption under the tongue occurs very quickly, with maximum plasma concentration reached within 5–8 min, reduced side effects, and increased patient adherence to treatment. Furthermore, the article explores the different types of sprays, including dosing, nasal, and oral sprays, and their applications in cardiovascular diseases, hypertension, headache, insomnia, and erectile dysfunction. The potential for future innovations in spray technology, such as nanotechnology for enhanced drug delivery, controlled release formulations, and specialized formulations for specific conditions, is also discussed. In conclusion, the article points out the promising prospects for the development of spray medications to optimize therapeutic approaches and improve patient outcomes in a wide range of diseases.

Keywords: Nasal sprays, Oral sprays, Dosage form

DOI: https://dx.doi.org/10.22159/ijap.2025v17i3.53398 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

According to the Ministry of Health, the overall morbidity rate in Russia increased over the three years leading up to 2023. In 2020, the total morbidity for all diseases was 155,097.9 cases per hundred thousand population; in 2021 it was 166,521.2 cases per hundred thousand population; and in 2022 it was 173,141.6 cases per hundred thousand population.

For newly diagnosed cases, this fig. (measured in cases per hundred thousand populations) also rose during these three years: in 2020 there were over 75.3 thousand cases, in 2021 over 84.9 thousand cases, and in 2022 over 88.9 thousand cases.

The majority of medications on the pharmaceutical market in Russia, according to the state register of medicines, are represented by tablets and parenteral drug forms, while tablets can be difficult for elderly patients and those suffering from dysphagia to swallow. Additionally, tablets need to be taken with a large amount of water, which is extremely inconvenient in critical situations. At the same time, injectable medications have drawbacks such as pain and discomfort during administration, risk of infection, the need for special preparation, and storage complexities. These listed drawbacks lead to difficulties and decreased patient adherence to therapy.

In light of this data, the development of effective and convenient Drug Forms (DF) is an urgent task today. Currently, there are numerous pharmaceutical products available in various dosage forms; however, many of them have low bioavailability of the active ingredient, are inconvenient for a large number of people, require additional steps before administration, and are difficult to dose. One promising approach to the development of dosage forms for the treatment of several diseases requiring rapid therapeutic effects is the use of spray dosage forms, as their application allows for the delivery of the drug directly into the systemic circulation, bypassing the gastrointestinal tract, and does not require additional actions before use. This can lead to a faster onset of the drug's action, reduced side effects, and increased patient adherence to treatment. This innovative solution offers several advantages, such as ease of use, accuracy in dosing, and a high profile of efficacy and safety. Understanding and evaluating the benefits of spray dosage forms in systemic therapy will allow for the optimization of treatment approaches and the development of new medications that contribute to more effective treatment of a wide range of diseases.

The aim of this article is to analyze existing research, evaluate the effectiveness of spray dosage forms in systemic therapy, and determine their applicability and potential for practical use [1].

According to the State Pharmacopeia, 15th edition: "Sprays are a dosage form consisting of a solution, emulsion, or suspension, the release of active substances from which occurs due to air pressure created by a mechanical pump-type aerosol dispenser or by comprising a polymer container, ensuring the release of the contents as a dispersion of solid or liquid particles in the air, the size of which corresponds to the route of administration" [2]. This allows for precise dosing and even distribution of the active substance on the surface or within the body cavity.

Methods: literature search

A thorough investigation was conducted in electronic databases such as PubMed, Scopus, Google Scholar, and e-library to identify publications in both Russian and English. The search covered all publications from 1990 to 2024, serving as a comprehensive reference for the development of spray dosage forms in cases of hypertensive crises, arrhythmias, migraines, cognitive disorders, and erectile dysfunction. The search criteria included terms such as spray, intranasal delivery, formulation development, oral spray, and sublingual delivery, either alone or in combination with drug names and disease titles. The authors excluded studies without full text, studies in languages other than English and Russian, and conference abstracts.

Historical reference

The first appearance of this dosage form was in 1888 in Toledo, Ohio. In search of an effective way to treat sore throats, Dr. Allen De Vilbiss set out to invent a revolutionary device. De Vilbiss's invention became a breakthrough in medicine. The idea was to create a convenient spray device with a long tube ending in a nozzle on one side and a rubber bulb on the other. The tube is immersed in a container with the medication, and the bulb allows for easy application of the medication to the desired area. This device is called an atomizer. Thus, thanks to the innovative ingenuity of Dr. De Vilbiss, patients no longer experienced discomfort when using medications in liquid form. The new device allowed for effective delivery of the medication to the affected areas of the throat, thereby improving treatment outcomes and alleviating the suffering of patients.

Advantages and disadvantages of sprays

One of the main advantages of the spray dosage form is the ability to accurately dose the active ingredient. With a special sprayer, the amount of medication that reaches the surface of the skin or mucous membranes can be controlled. This is especially important when treating children or patients with weakened health, where precise dosing plays a crucial role. Another advantage of sprays is the rapid and effective delivery of the active ingredient into the body. The aerosolized particles instantly reach the desired surface and are quickly absorbed through the skin or mucous membranes. This significantly reduces the waiting time for the effect. For example, the well-known nitroglycerin spray reaches its maximum effect within 1-2 min compared to 5-7 min for the tablet form. Moreover, the spray resulted in a decrease in blood pressure of 20 mm Hg within the first 5 min, whereas the tablet caused a similar decrease only after 10 min [3]. Sprays also offer a high degree of convenience. They are compact, lightweight, and easy to apply. Because of this, sprays can be carried at all times and used whenever necessary. Additionally, the aerosolization of the medication allows for even coverage of the surface and prevents potential smearing or staining. Moreover, sprays provide the possibility of applying the medication to hard-to-reach areas. For example, a spray can be used to treat throat or nasopharyngeal conditions when traditional forms (tablets or drops) may not be effective. Sprays can also be used to apply medication to large areas of skin when treating wounds or burns. In addition to the above, sprays have a long shelf life and good stability of the active ingredient. This is due to the design features of the sprayer and packaging. As a result, sprays can be used for an extended period without loss of quality and effectiveness.

However, there are some disadvantages to the spray dosage form, including:

- Low bioavailability: medications administered in sprays have low bioavailability, as they may not be fully absorbed by the mucous membranes. This can lead to reduced effectiveness and the need to increase the dosage.

- Local irritation: some medications administered as sprays may cause local irritation of the mucous membranes, leading to discomfort, pain, and tissue damage. To mitigate this drawback in the development of oral sprays, buffer solutions or emollients such as the following can be used:

Glycerin: This is polio widely used in the pharmaceutical and cosmetic industries as an emollient. It helps retain moisture in the skin and mucous membranes, making them softer and more elastic.

Propylene Glycol: This is a small polymer of glycerin that is also used as an emollient in medicinal sprays. It has moisturizing properties and can help prevent dryness and irritation of the mucous membranes.

Macrogol: This is a group of polyethylene glycols used as emollients in various pharmaceutical preparations. They possess moisturizing and softening properties and can help prevent dryness and irritation of the mucous membranes.

Polysorbate: This is an emulsifier that can also act as an emollient in medicinal sprays.

- Risk of systemic effects: when medications are delivered in sprays, there is a risk of systemic effects, as the drug may be absorbed into the bloodstream. This can result in side effects that may be more severe than those associated with local application.

- High cost: medications in sprays often cost more than other forms due to higher production and packaging costs.

Regulatory barriers (compliance with norms and standards: Good Manufacturing Practice (GMP), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use considerations (ICH) guideline Q8 (R2)) and high production costs remain significant obstacles to the widespread adoption of medicinal sprays. Streamlining manufacturing processes and developing cost-effective formulations are crucial for broader market penetration.

Reducing production costs can be achieved through:

Optimizing manufacturing processes: Implementing modern technologies and automating production processes can significantly lower costs. Utilizing high-tech equipment for mixing, filtering, and packaging can enhance efficiency and reduce waste.

Scaling up production: Transitioning to mass production allows for a decrease in the unit cost of products through economies of scale. Entering into contracts for larger volumes with raw material suppliers can also help reduce costs.

Using alternative materials: Researching and implementing cheaper and more accessible excipients and packaging materials can help lower overall production expenses.

- Risk of medication getting into the eyes. When using a spray, there is a risk of the medication accidentally entering the eyes, which can lead to irritation and tissue damage. There are several types of sprays, each with its characteristics and methods of application.

Types of sprays and their applications

One of the most common types of sprays is the metered-dose spray. In this type, the medication is contained in an aerosol container with a dispenser that ensures precise and even distribution of the active ingredient when the button is pressed. Metered-dose sprays are used to treat many conditions, such as asthma, Chronic Obstructive Pulmonary Disease (COPD), rhinitis, throat issues, and others. Another type of spray is nasal spray. They are designed for use in the nasal cavity and are often used to treat nasal congestion or allergic rhinitis. Nasal sprays help constrict blood vessels in the nose, reducing swelling and facilitating breathing. They may also contain antibiotics or steroids to combat infections or inflammation.

Typically, when we talk about sprays, we think of their local application; however, the most intriguing area of prospective systemic use for nasal sprays has become cardiovascular pathology. Intranasal (IN) administration has emerged as a new approach for rapid systemic absorption, potentially applicable in the treatment of cardiovascular events.

IN administration of cardiovascular pharmaceuticals was first proposed in 1994 by Landau and his colleagues [4]. However, there have been relatively few studies reported in the literature on the development of pharmacotherapy for the cardiovascular system using IN administration. Due to minimal scientific interest and progress in the following decades, this route of drug administration has remained largely unexplored. In delivery still represents a new and innovative approach to achieving systemic effects of drugs in cardiovascular diseases that require urgent therapeutic intervention, such as acute myocardial infarction, hypertensive crises, and cardiac arrhythmias [5–8]. The advantage of this non-invasive route is the rapid absorption of the drug through the nasal mucosa and quick systemic circulation, as it bypasses first-pass metabolism and/or gastrointestinal disturbances that hinder oral administration [4]. The nasal mucosa is characterized by extensive vascularization with a relatively large absorption area due to the porous and thin basal membrane of the nasal endothelium [9]. All of the aforementioned properties of the nasal mucosa, which lead to its high permeability, ensure more effective and rapid systemic absorption of the drug, even in small amounts compared to oral administration [10]. IN delivery can be considered equivalent to intravenous administration [11, 12]. Furthermore, IN administration can be self-administered by patients at home, which avoids the need for constant medical supervision.

Self-administering medication through the nose is easy, allowing individuals to control their medical needs [13]. Hypertension is one of the most common pathologies of the cardiovascular system. At the same time, it is one of the most difficult conditions to treat. The most dangerous manifestation of arterial hypertension is a hypertensive crisis, which requires immediate intervention.

Hypertensive Crises (HC) are characterized by pronounced spikes in blood pressure, accompanied by damage to vital organs. Endothelial damage to blood vessels develops; leading to a cascade of

detrimental consequences if timely treatment is not initiated [14]. HC most often occurs in individuals with pre-existing arterial hypertension, irritated systemic vascular resistance, and inadequate autoregulation of cerebral blood flow [15]. Urgent treatment of HC is necessary, but excessive and abrupt lowering of blood pressure should be avoided. Therefore, the onset of the drug's action must be rapid and continuously monitored. To date, effective acute therapy for HC remains a subject of research and largely depends on the underlying condition. Previously used Calcium Channel Blockers (CCB) were associated with dangerously rapid drops in blood pressure [16]. However, nifedipine, a CCB of the dihydropyridine subclass, remains a first-line drug for women with preeclampsia [17]. In administration of nifedipine was evaluated by Kubota *et al.* (2001) [18] in healthy volunteers with acute blood pressure reduction at a dose of 8.12±0.32 mg. The study showed that IN administration demonstrated the most favorable early increase in serum concentration and effectively reduced blood pressure compared to oral or sublingual routes.

Table 1: Pharmacokinetic parameters after administration of 10 mg nifedipine via different routes of administration

Route of administration	Cmax (ng/ml)	Tmax (min)	AUC (ng·h/ml)	Ref
Oral	50.5±10.1	64.2±13.5	177.1±88.6	[18]
Sublingual	61.8±5.4	77.8±14.4	434.0±96.7	
Intranasal	42.9±5.6	55.7±12.3	211.3±48.9	

Similar results were obtained for another dihydropyridine CCB, isosorbide dinitrate, which was found to have better hemodynamic effects than oral and tracheal delivery methods. In the groups where oral and nasal administration methods were used, systolic blood pressure decreased by 10% (orally) and 17% (nasally) after 4 min ($P<0.05$) and returned to baseline after 20 min. Diastolic blood pressure decreased in both groups after 4 min ($P<0.05$). Heart rate significantly increased in the IN delivery group ($P<0.05$) and continued to change up to 60 min after drug administration. In both groups, PaO2/FIO2 decreased by 14% and 9% after 10 min ($P<0.01$). In the tracheal group, plasma concentration did not increase, and these hemodynamic changes were not observed [5, 19]. The main issues with the IN administration of isosorbide dinitrate solution were dose inconsistency and low bioavailability of the fraction of the dose reaching the gastrointestinal tract through the internal nasopharynx [18]. These are common problems with nasal delivery, highlighting the need for innovative formulations with targeted deposition and more effective absorption in the nasal cavity [20]. If the use of intensive short-acting forms is avoided, CCB still have the potential to regain their place in therapeutic algorithms for hypertension peaks or crises [21]. Historically, beta-blockers have been among the most frequently prescribed first-line medications for hypertension, but their use is currently limited [22]. Among β-blockers, carvedilol, timolol, and propranolol have been preclinical evaluated [5, 23-25]. The study by Kar and Singh (2023) applied a Design of Experiments (DOE) methodology to develop and optimize cationic nanoliposomes loaded with carvedilol in the form of an in situ nasal gel using P90H and DOTAP Cl (cationic) lipids. A comparative pharmacokinetic study of oral carvedilol suspension and oral cationic liposomes, as well as liposomes incorporated into the in situ nasal gel, revealed the superiority of the nasal formulation. In particular, nearly a sevenfold increase in the drug's C (max) in rabbit plasma and a one-hour earlier T (max) was observed for the in situ gel compared to the pure drug and orally administered liposomes. Additionally, a fivefold higher relative bioavailability compared to the oral carvedilol suspension was calculated [23].

Another application point for the use of nasal spray in cardiology has been Paroxysmal Supraventricular Tachycardia (PSVT). The nasal spray "Etripamil" (Milestone Pharmaceuticals, Montreal-Saint-Laurent, Quebec, Canada) is a non-dihydropyridine calcium channel blocker of the short-acting phenylalkylamine class. It works by slowing down Atrioventricular (AV) node conduction and prolonging the refractory periods of the AV node by inhibiting the influx of calcium ions through slow calcium channels in the AV node cells [25]. Serum esterase metabolizes the drug into an inactive carboxylic acid. The intranasal formulation has high efficacy: the time to reach maximum plasma concentration is about 8 min, and the average half-life is about 20 min. The rapid onset and offset of action allow for immediate use of the drug and help avoid potential complications associated with long-acting therapies. The RAPID study showed: 64.3% of etripamil patients experienced PSVT termination within 30 min compared with 31.2% of placebo patients (Hazard Ratio (HR): 2.62; 95% Confidence Interval (CI): 1.66–4.41; $p<0.001$). The median time to conversion was also significantly better with verapamil (17.2 vs 53.5 min) [27].

Considering the unpredictable, recurrent, and debilitating nature of paroxysmal supraventricular tachycardia, clinical studies have demonstrated that IN administration of Verapamil is a potentially safe and convenient outpatient option for patients. IN Verapamil not only has comparable efficacy to modern parenteral medications but also helps avoid the deep systemic side effects associated with intravenous drugs [28, 29]. The combined analysis of NODE-301 and RAPID showed that verapamil resulted in a lower number of patients seeking medical assistance (25% vs. 15%; $p = 0.013$) or being admitted to the emergency department (22% vs. 14%; $p = 0.035$). Although treatment-related side effects were more common with verapamil (50% vs. 11%), most were mild and transient. No significant safety issues were reported, despite the increased exposure to the drug considering the double dosing protocol aspect [27].

In administration has emerged as a promising method for drug delivery in cardiovascular pathology, offering a non-invasive and potentially effective way to bypass traditional routes. This method is particularly attractive for some cardiovascular drugs, given its potential to enhance bioavailability and reduce the need for invasive procedures. However, it is essential to acknowledge that the use of IN for delivering cardiovascular drugs is not without challenges. Drawbacks such as variable absorption rates, irreversible damage to the nasal mucosa, and the limited volume of drugs that can be delivered necessitate careful evaluation.

Additional common issues include the stability of liquid formulations and the accidental delivery of the drug to the lungs. The choice of drug type and excipients is determined by factors such as the solubility and stability of the active ingredient, as well as the required concentration to deliver an effective dose in a typical range of 25 to 250 ml of spray [30].

Currently, a nasal spray for migraine containing sumatriptan, which also has systemic effects, is very popular in the Russian pharmaceutical market. The clinical efficacy of triptans depends on the route of administration, with the highest efficacy achieved through IN and subcutaneous administration of the drug. In one previous study, the nasal spray of zolmitriptan in the dose range of 0.5–5 mg was found to be more effective than 2.5 mg zolmitriptan tablets and placebo, both in terms of onset of action and the number of patients achieving a positive treatment outcome [31]. In subsequent studies conducted in real clinical practice, the 5 mg nasal spray of zolmitriptan significantly reduced headache intensity within 10 min, and after 2 h, the number of patients with a positive treatment outcome was significantly higher than with placebo [32].

In a prospective multicenter observational Russian study conducted in 2023, the results of previous trials of zolmitriptan nasal spray were confirmed in both children and adults, demonstrating its efficacy at a rate of 70%. The absence of headache or mild intensity was recorded as early as 10 min in 25% of patients (the earliest assessment in this study) and 28% of patients after 30 min post-administration. Two hours after the application of the 2.5 mg zolmitriptan nasal spray, the number of patients with a positive treatment outcome across all three consecutive migraine attacks was 69.2%, 75%, and 75%, respectively. The zolmitriptan nasal spray was well tolerated, with most adverse events being transient and mild [33].

Numerous studies have also been conducted comparing the efficacy of oral sumatriptan and nasal spray. The efficacy of nasal spray sumatriptan (20 mg) and zolmitriptan (5 mg) was comparable to that of oral sumatriptan (100 mg) [34].

Table 2: Pharmacokinetics of sumatriptan by different routes of administration

Route of administration	Dosage (mg)	Maximum 24 H dose (mg)	Time of peak levels	Elimination half-life (H)	Bioavailability (%)	Ref
Subcutaneous	6	6	12 min	2	97	[35]
Oral	50-100	200	2-3 h	2	15	
IN	20	40	1 h	2	17	

The results of the systematic review show that subcutaneous administration of sumatriptan is the most effective method for treating migraines. Nearly 59% of participants who received 6 mg of sumatriptan experienced a reduction in pain from moderate or severe to none within two hours, compared to only 15% in the placebo group. The Number Needed to Treat (NNT) was 2.3 (with a 95% confidence interval of 2.1–2.4) among 2,522 participants. Oral, rectal and IN forms of sumatriptan also provided clinically significant pain relief. For example, an oral dose of 50 mg resulted in complete pain relief for 28% of participants, compared to 11% in the placebo group (NNT 6.1 with a 95% confidence interval of 5.5–6.9 among 6,447 participants). Subcutaneous administration provided faster pain relief compared to other methods. It was also noted that early administration of the medication when the pain was mild was more effective than waiting for the pain to become moderate or severe [35]. The proportions of patients, who experienced pain relief with oral rizatriptan, oral almotriptan, and nasal spray sumatriptan were 10.7 mg, 17.8 mg, and 25.4 mg, respectively, which were close to the corresponding maximum approved doses [36].

Another type of spray is oral spray. They are applied directly to the mucous membrane of the mouth. Oral sprays may contain antiseptics, analgesics, agents for cardiovascular pathology, or anti-inflammatory components [37].

The oral cavity, with its highly permeable mucous membranes, has long been used for drug delivery into the systemic circulation (oral transmucosal delivery) and for local delivery to underlying tissues (delivery through the oral mucosa). The process of introducing an active substance and a dosage form intended for the release of the drug in the oral cavity is known as the oral delivery system or intraoral dosage form.

The first evidence of effective drug absorption through the buccal mucosa was recorded over 100 years ago. In 1879, it was noted that sublingual administration of nitroglycerin successfully alleviated the symptoms of classic angina pectoris. Since then, drug delivery through the mucous membrane of the oral cavity has become the subject of increasing interest due to its potential advantages over other delivery methods. The concept of aerosol emerged as early as 1790 when carbonated beverages were introduced in France under pressure.

Drugs are often delivered through the mucous membrane of the oral cavity in three different forms:

- Sublingual drug delivery: administration through the layer on the anterior surface of the tongue and, consequently, the floor of the mouth.
- Transbuccal drug administration: primarily consists of the buccal mucosa and, therefore, the BM membrane.
- Local drug delivery: consists of administration in all areas of the oral cavity except the two previous zones.

Oral spray has several advantages over other dosage forms, such as tablets, capsules, effervescent tablets, dry syrups, and chewing gums, which are commonly used to enhance patient compliance. The intake of effervescent tablets/granules and dry syrups involves inevitable preparation, including the intake of water. Elderly patients may struggle to chew large pieces of tablets or chewable gums and may sometimes experience a bitter or unpleasant taste of the drug in these dosage forms. An oral spray includes rapid release of the active substance in the form of micro-sized droplets into the oral cavity for absorption by the oral mucosa. As a result, we achieve direct and rapid dispersion of the active substance solution over the maximum possible area of the oral mucosa, where absorption occurs. Since the released drug is in the form of fine droplets, water is not required upon administration.

The first commercially successful sublingual spray was Nitroglycerin lingual spray (marketed as Nitrolingual® Spray in the USA). Lingual sprays of other nitrate esters, such as isosorbide dinitrate and mononitrate, have also been reported, but due to the need for a larger dose, these lingual sprays were not as medically interesting as the nitroglycerin lingual spray. Patents [38, 39] in this field and published literature indicate that the absorption of nitroglycerin from the tongue occurs very rapidly, with maximum plasma concentration (Cmax) reached within 5-8 min, followed by a similarly rapid decline in these levels within 30 min.

To date, various oral sprays are available on the pharmaceutical market, including those that act systemically, for example:

Table 3: Oral sprays on the pharmaceutical market

Dosage form	Active ingredient	Commercial name	Indications	Features of the drug	T max (min)	Bioavailability (%)	Side effects
Buccal spray	Recosulin	Oral-Recosulin	for the treatment of type-1 and type-2 diabetes	-	30	10	-
Mouth spray	Nicotine	Nicotrol® Inhaler	Tobacco cessation	Despite the name, this product is delivered via the oral trans mucosal route. Most of the nicotine is deposited in the mouth with less than 5% reaching the lower respiratory tract.	15	<5	may be toxic and addictive
Lingual Spray	Zolpidem	Zolpimist	Short-term treatment of insomnia	NovaMist™ delivery Technology	0,9 H	~70	Nausea, fatigue, headache
Sublingualspray	Nitroglycerin	Nitromist	To treat or prevent attacks of chest pain(angina)	-	8	100	dizziness, headaches, pre-fainting state
Sublingual spray	Isosorbide dinitrate	Изакардин	Management and prevention of angina attacks, including before exercise; acute myocardial infarction and post-infarction rehabilitation	-	30 sec	60	headaches, orthostatic hypotension, burning tongue
Oral spray	Sildenafil citrate	Джент	indicated for erectile dysfunction	-	60	~40 (from 25 to 63%)	Headache, dizziness, nasalcongestion

Human buccal insulin spray with Deoxyribonucleic Acid (DNA), created using Generex Biotechnology's Rapid Mist technology for insulin delivery, is effective in treating type 1 and type 2 diabetes. The main advantage of this insulin spray is that patients with diabetes will no longer need to inject insulin. The spray provides a rapid effect and ensures a very high pharmacodynamic profile with no pain upon administration by patients [40].

Nicotrol® Inhaler. The proposed method of drug delivery is expected to improve the treatment of nicotine dependence with minimal side effects in the coming years [41].

Zolpimist (Zolpidem Tartrate). This oral spray is used for the treatment of short-term insomnia caused by difficulty falling asleep. Controlled clinical studies have shown that zolpidem tartrate reduces sleep onset latency for up to 35 days. Clinical trials to confirm efficacy lasted 4–5 w, with a formal sleep test at the end of treatment. Zolpimist is released as a clear, colorless solution with a cherry flavor, designed to be sprayed directly onto the tongue. A single spray delivers 5 mg of zolpidem tartrate [42].

Nitro mist spray is a nitrate vasodilator. Sublingual spray, 400 mcg [3].

The Izacardin® preparation in spray form is intended for application to the mucous membrane of the oral cavity. It is used for the relief of angina attacks or before physical or emotional stress that provokes the attack, as well as in acute myocardial infarction or acute left ventricular failure (to be used under medical supervision with monitoring of blood pressure and heart rate).

Gent oral spray. Results from a clinical study showed that the use of sildenafil citrate in spray form leads to a faster onset of action in patients with endothelial dysfunction compared to the tablet form. The effect of the agent manifests 1.7 times faster according to the AVSS-Andros can test results. 62.5% of patients reported an improvement in erectile function within 24 h after taking the liquid form of the medication, while 25% reported improvement after taking the tablet form. Furthermore, the liquid form of sildenafil is characterized by a residual effect that contributes to the improvement of erectile function for 24 h after taking the medication. These results open new prospects for effective treatment of erectile dysfunction symptoms in clinical practice [43].

There are also topical sprays used for the treatment of various skin conditions such as eczema, psoriasis, and burns. These sprays contain active ingredients that help moisturize and soothe the skin, as well as accelerate the healing process.

One of the features of sprays is that they allow for the direct delivery of the active substance to the surface of the affected area. This enables a rapid therapeutic effect and reduces the negative impact on other organs or systems of the body.

Prospects for development and innovations in the field of sprays

In recent years, there has been significant progress in the development of sprays, opening new prospects for their use. One of the main innovations is the creation of sprays with improved characteristics, such as more precise dosing and more effective penetration of the active substance into the body.

For example, recently developed sprays with nanoparticles of the active substance allow for increased bioavailability and faster onset of drug action. This is particularly beneficial in the treatment of upper respiratory tract diseases, as nanoparticles can reach hard-to-access areas of the mucous membrane and exert a more effective impact.

The advantages of using nanoparticles as drug carriers are attributed to two key characteristics: their tiny size and the use of biodegradable materials in most cases [44, 45]. It has been established that the effectiveness of most drug delivery methods largely depends on particle size. Nanoparticle drug formulations possess enhanced solubility and superior bioavailability, which result from their small particle size and large surface area [46].

In a 2022 study, researchers succeeded in developing a Nano emulsion spray of tadalafil for the treatment of pediatric pulmonary arterial hypertension using a nebulizer. An optimal formulation was developed that has the necessary effective dose of the drug (2.45 mg/ml) and globule size (25.04 nm), suitable pH, and can be aerosolized using a jet nebulizer. Moreover, the formulation demonstrated stability after sterilization and a favorable safety profile confirmed by both *in vitro* and *in vivo* toxicity studies [47].

The study 2021 developed a new nano spray formulation utilizing a Self-Nano Emulsifying Drug Delivery System (SNEDDS) to enhance the bioavailability and efficacy of a combination of melastomamalabathricum extract and gentamicin. The authors conducted a thorough characterization of the resulting product, including pH analysis (5.61±0.16), emulsification time (7.68±0.18 seconds), particle size (270.7 nm), and zeta potential (-37.20 mV), indicating the stability of the formula.

The results showed that the Nano spray possesses stable characteristics and that its emulsion releases active substances more rapidly compared to the non-formulated variant. This makes it a promising candidate for clinical applications. This delivery system may be particularly beneficial for enhancing therapeutic effects and reducing side effects in the treatment of infectious diseases. The study emphasizes the importance of synergistic combinations in the development of effective pharmaceutical formulations [48].

A 2022 review described paroxetine delivered IN as a Nano emulsion through the olfactory region [49].

Key findings

Behavioral Activity: The Nanoemulsion significantly improved behavioral activity compared to the paroxetine suspension.

Biochemical Effects: The Nano formulation notably increased reduced glutathione levels and decreased elevated levels of Thiobarbituric Acid Reactive Substances (TBARS).

These results highlight the potential of using Nanocarrier systems to enhance the therapeutic effects of medications in treating cognitive dysfunction in depression.

Another promising innovation is the creation of sprays with controlled release of the active substance. Such sprays can be used for long-term treatment of chronic diseases where a continuous supply of small doses of medication is necessary to maintain a stable concentration level in the body.

Overall, the prospects for development and innovation in the application of sprays represent a significant interest in medicine. With new technologies and approaches, we can expect the emergence of more effective and safer drug formulations that will help improve the quality of treatment for various diseases and enhance patient comfort during their use.

CONCLUSION

Research conducted in this area shows that sprays represent a new, effective form of drug delivery into the body. Sprays possess unique properties that allow them to easily and evenly distribute over the surface to which they are applied. As a result, the active substances contained in sprays can be absorbed more effectively and quickly, which is particularly important in systemic therapy.

Furthermore, sprays significantly expand the range of medications that can be delivered through the skin or mucous membranes of organs. This is important for treating conditions that traditionally require systemic therapy, such as those described above in cardiovascular pathology. Thanks to sprays, we can deliver substances that cannot be administered through conventional routes, thereby substantially improving treatment efficacy and increasing the chances of patient recovery.

Additionally, sprays offer a high degree of user convenience. They are portable, easy to apply, and do not require special skills for use. This is especially important for patients suffering from chronic conditions who need to receive systemic therapy regularly. The use of sprays can significantly simplify the procedure and improve the quality of life for such patients.

Thus, sprays represent a new promising approach to systemic therapy. Further research in this area will help improve existing treatment methods and enhance the quality of medical care for patients.

ACKNOWLEDGMENT

The authors express their gratitude to the Federal State Autonomous Educational Institution of Higher Education I. M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University)

FUNDING

Nil

AUTHORS CONTRIBUTIONS

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

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